Roles & Responsibilities of the Sponsor

Sponsored by
Center for Cancer Research
National Cancer Institute

Objectives

Funding for clinical research comes from the federal government or the private sector. In addition to providing financial resources, some funding groups also provide the investigational agent. They are referred to as the Sponsor and are responsible for the initiation and management of a new agent under the FDA's Investigation New Drug (IND) Application (Title 21 Part 312). This module will review the role of the IND sponsor.

At the conclusion of this module, you will be able to:

- Define what is meant by a "sponsor"
- List the 4 broad areas of sponsor responsibilities
- Describe the purpose of FDA Form 1571
- List 5 items that are submitted with an initial IND application

Who is a Sponsor?

- The sponsor can be:
  - Individual
  - Pharmaceutical company
  - Government agency
  - Academic institution
  - Private organization
  - Other organization

Definition of Sponsor….

- “An individual, company, institution or organization which takes responsibility for the initiation, management, and / or financing of a clinical trial.” (ICH)
- “A person who takes responsibility for and initiates a clinical investigation. … The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator.” (CFR)

….Definition of Sponsor

- In general, the sponsor is the commercial manufacturer that has developed a product in which it holds the principal financial interest
- Holds the IND (Investigational New Drug) application and files the NDA / BLA (New Drug Application/Biological Licensing Application)

Drug/Biologic Development

- Discovering and developing safe and effective drugs is more promising as our knowledge of disease increases
  - Human genome sequencing
  - Increase understanding of disease at the molecular level
  - Advances in genomics and proteomics
  - Advances in informatics (i.e. computational power)
- Researchers work to:
  - validate the targets
  - discover the right molecule (potential drug/biologic) to interact with the target chosen
  - test new compound in the lab and clinic for safety and efficacy
  - gain approval and get the new drug into patients

What is a Drug?

- Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease
- Articles (other than food) intended to affect the structure or any function of the body of man or other animals
- Articles recognized in the official U.S. Pharmacopeia, National Formulary, Homœopathic Pharmacopœia of the U.S. or any supplement to any of them

Food Drug and Cosmetic Act, sec. 201(g)(1)

What is a Biological Product?

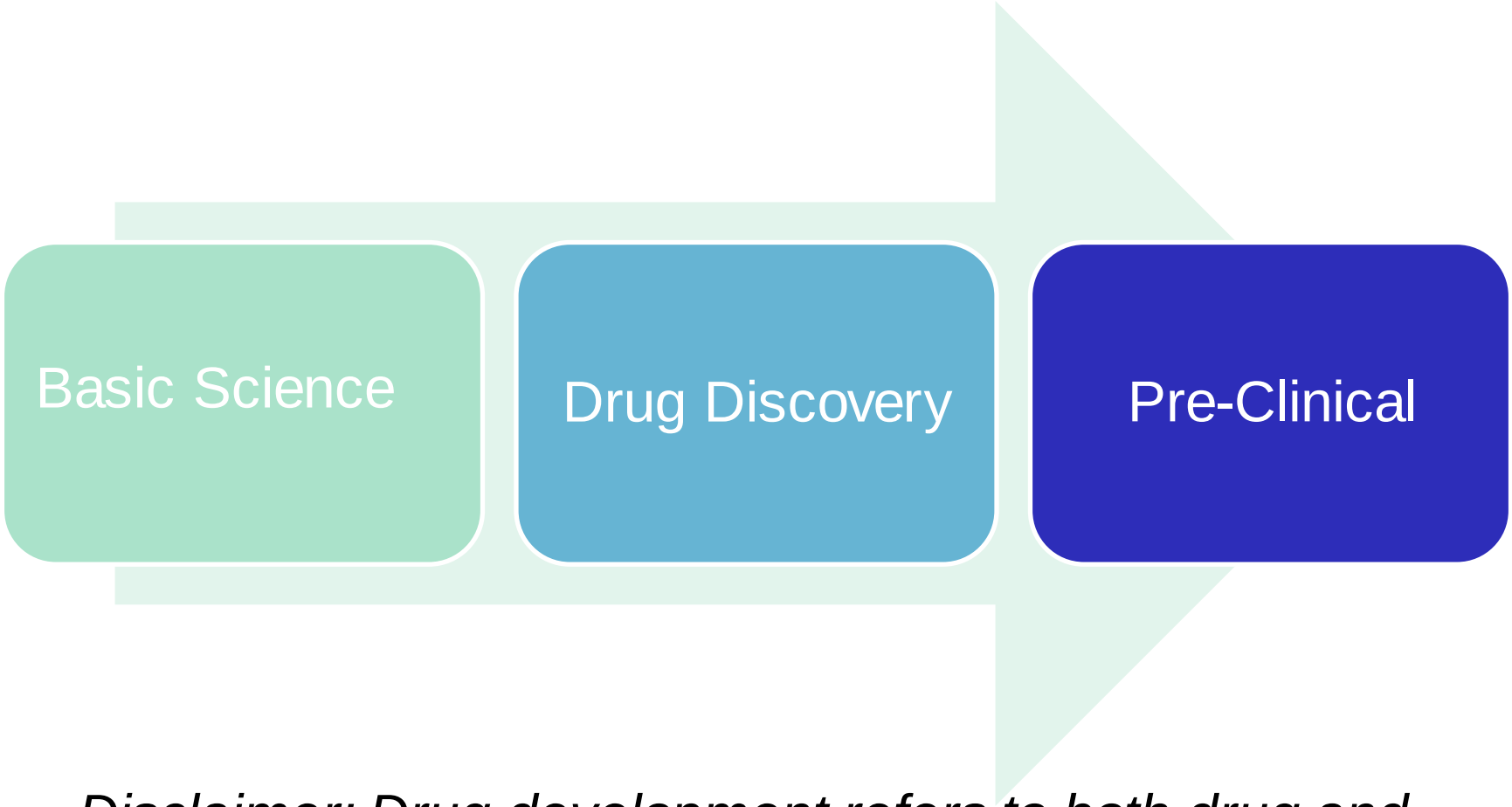
- "…virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, … applicable to the prevention, treatment, or cure of a disease or condition of human beings."

Section 351 of the Public Health Service (PHS) Act

Public and Private Collaborations

- Roles are interdependent to translate basic research into interventions
- Biopharmaceutical companies are primary source of R&D
- NIH:
  - Provides leadership and funding support to universities, medical schools, research centers and other non-profit institutions
  - Stimulates basic research and early stage development

Finding a Drug



Disclaimer: Drug development refers to both drug and biologic agents

Basic Science…

- Understand the disease to be treated
- Unravel the underlying cause of the condition
- Understand how the genes are altered
  - How that affects the proteins
  - How those proteins interact with each other
  - How those affected cells change the specific tissue they are in
  - How the disease affects the entire patient

…Basic Science

- Choose a molecule to target
  - Typically a single molecule (e.g., gene or protein) which is involved in a particular disease
  - Target needs to be one that can potentially interact with and be affected by a drug/biologic
- Test the target and confirm its role in the disease

Drug Discovery

- Find the lead compound
  - A promising molecule that could become a drug by acting on the target to alter a disease
- Complicated, time-consuming and costly process
  - 5-20 years
  - For every 5,000- 10,000 compounds that enter the research and development (R&D) pipeline, **ONE** receives approval
  - Estimated to be $800 million to $1 billion
    - Includes the cost of the thousands of failures

Sources of Drugs

- Plant
- Animal
- Mineral
- Microbiology
- Semi-synthetic/Synthetic
- Recombinant DNA

Naming of Drugs

- Chemical name
  - Scientific name based on the compound's chemical structure
  - Almost never used to identify the drug in a clinical or marketing situation
- Generic name
  - Granted by the International Union of Pure and Applied Chemistry (IUPAC)
  - Commonly used to identify a drug during its clinical lifetime
  - Appears with the company's trade name on drug labels, advertisements, and other information
- Brand name (Trademark)
  - Created by the company that patents the drug
  - Identifies the drug during the years that the company has exclusive rights to make, sell, and use

Sponsors Responsibilities: 4 Broad Areas

- Preclinical / non-clinical
- Manufacturing
- Clinical
- Post-approval
- May use a CRO (Contract Research Organization)

Preclinical Goals

- Find a product
  - Pharmacological activity
  - Reasonably safe
- Conduct pre-clinical studies
  - animal pharmacology, toxicology, and carcinogenicity

Preclinical Studies

Purposes of PRECLINICAL studies are to:

- Determine the optimal formulation of the product
- Select an initial safe starting dose for human trials
- Identify potential target organs of toxicity
- Recommend appropriate types of clinical monitoring

Manufacturing Responsibilities

- Obtain manufacturing information:
  - Characterization of the product
  - Preliminary stability studies

Clinical Responsibilities

- Submit & maintain Investigational New Drug Application (IND) with FDA
- Conducting Phase 1, 2, 3 Clinical Trials
- Submit New Drug Application (NDA) to FDA for drugs
- Submit Biological License Application (BLA) to FDA for biologics

Investigational New Drug Application (IND)

- Sponsor submits to the FDA
- Descriptive notification of intention to conduct clinical studies with an investigational drug or biologic
- Allows for transportation of product (non-approved drug) across state lines

IND Sections

- FDA Form 1571
- Table of contents
- Intro statement
- General investigative plan
- Investigator's Brochure (IB)
- Clinical protocols
- CMC (chemistry manufacturing and control) data
- Pharmacology & toxicity data
- Previous human experience
- Additional information

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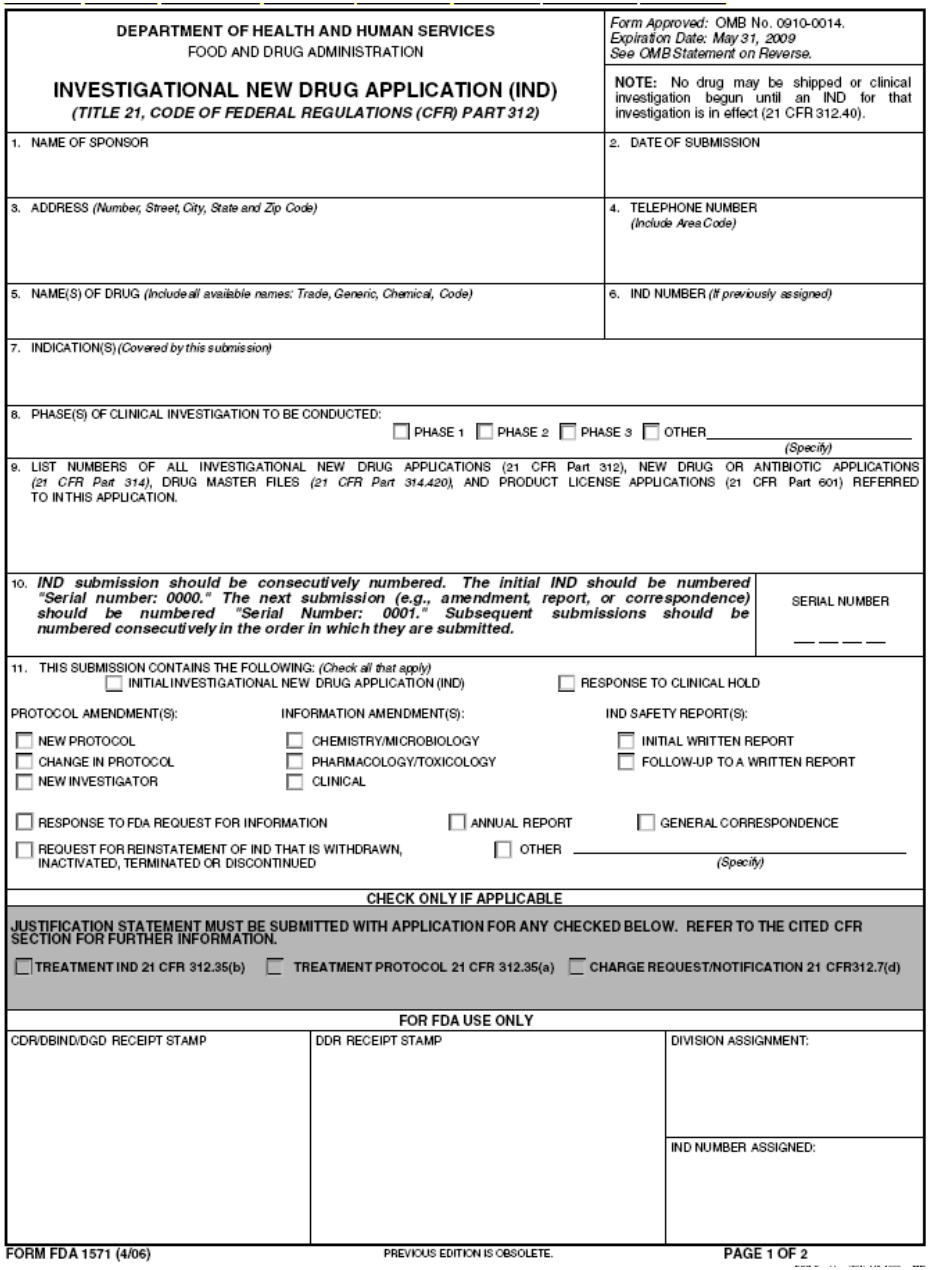
Submitted with the initial IND submission and each subsequent submission to the IND



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: May 31, 2009
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
2. DATE OF SUBMISSION
3. ADDRESS *(Number, Street, City, State and Zip Code)*
4. TELEPHONE NUMBER *(Include Area Code)*
5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
6. IND NUMBER *(If previously assigned)*
7. INDICATION(S) *(Covered by this submission)*
8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
   ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.
10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.*** SERIAL NUMBER ___ ___ ___ ___
11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
    ☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

FORM FDA 1571 (4/06) PREVIOUS EDITION IS OBSOLETE. PAGE 1 OF 2

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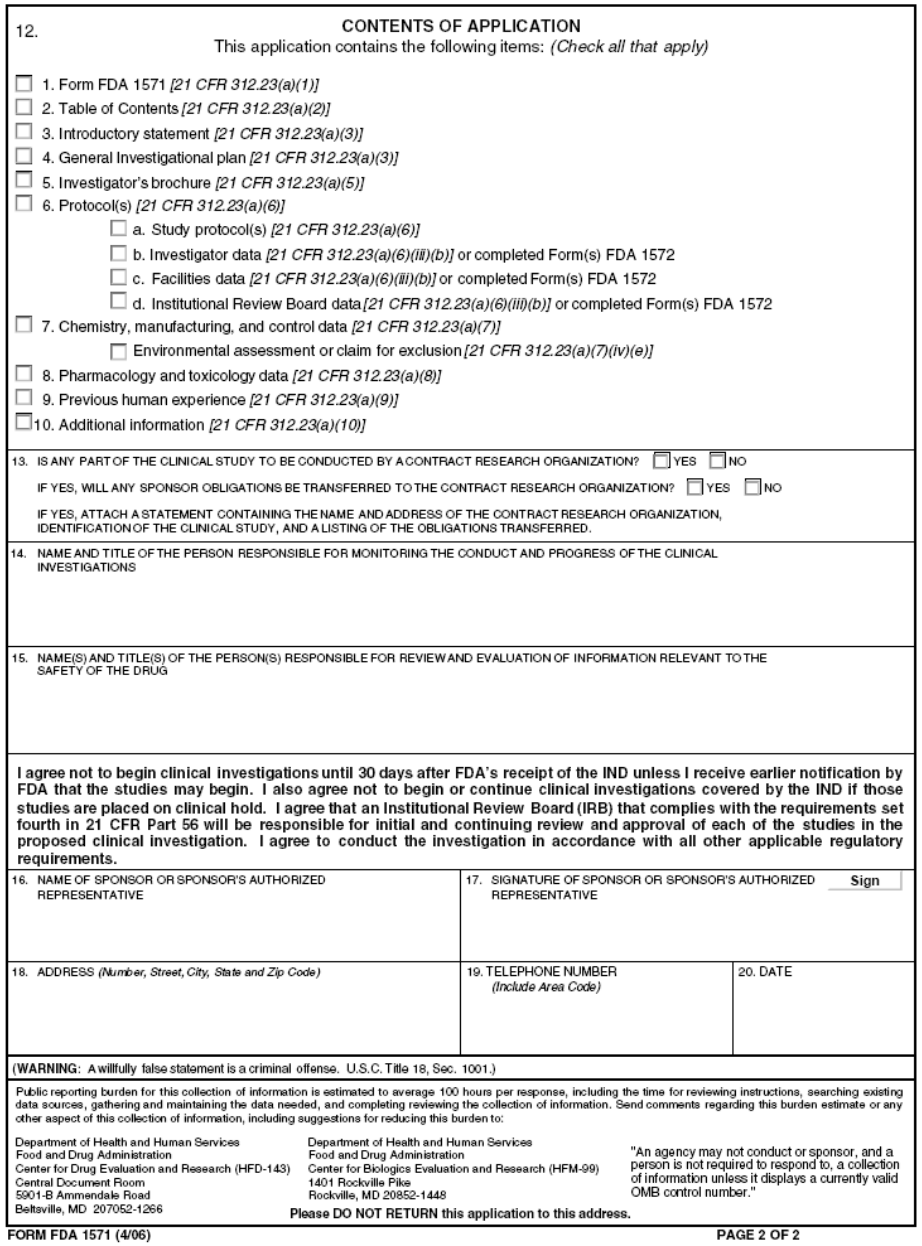
The FDA has 30-days to review the protocol. FDA will not contact sponsor if all is OK to proceed, only if a "hold" is needed.



12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE Sign	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-143)
Central Document Room
5901-B Ammendale Road
Beltsville, MD 207052-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

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Conducting Clinical Trials

- Selecting qualified investigators and monitors
- Informing Investigators
- Reviewing ongoing studies
- Record keeping and record retention
- Ensuring the return or disposition of unused investigational drug supplies

Investigator Selection

- Assess qualification of PI and Sub-investigators
  - Qualified by training & experience
  - Ability to supervise administration of product
  - Investigational Product shipped to them
- Assess site (physical plant capabilities). Examples:
  - Is there adequate pharmacy space for drug storage?
  - Are there SOPs for freezer alarms?

Informing Investigators

- All investigators must be fully informed of investigational product research findings
  - Investigator Brochure
  - Reprints / published articles
  - Reports / letters to investigators
  - IND Safety Reports

Review Ongoing Investigations…

- Investigator compliance - is conducting the study in compliance, with the protocol, with the Federal Regulations, and with GCP?
- Is there unreasonable & significant risk to the study subjects?
- Monitor clinical trial conduct
- Medical Monitor - individual responsible for the development and oversight of all clinical trials in a portfolio of study agents

…Review of Ongoing Investigations…

- Review and evaluate
  - Safety and effectiveness data
- Provide FDA
  - Annual reports
  - Summary of accrual statistics, safety, toxicity and efficacy data, as well as ongoing non-clinical and manufacturing progress

Potential Actions for Non-compliance

- Secure compliance

  OR
- Stop product shipments to the investigator
- Terminate the investigator's participation in the study
- Secure return or disposal of investigational product

Actions for Unreasonable and Significant Risk

- Stop clinical trial: permanent vs. temporary
- Notify the FDA, all IRBs, all investigators of the risk(s)
- Assure the disposition of all outstanding product or resume trial with amendment
- Provide FDA full report on actions taken

Monitoring of Clinical Trials…

- Monitoring function may be performed by:
  - The sponsor
  - Contract staff

…Monitoring of Clinical Trials…

Sponsor may designate 1 or more appropriately trained and qualified individuals from various backgrounds to monitor the trials

MD's

Nurses

CRA's

Pharmacists

Engineers

Paramedical Professionals

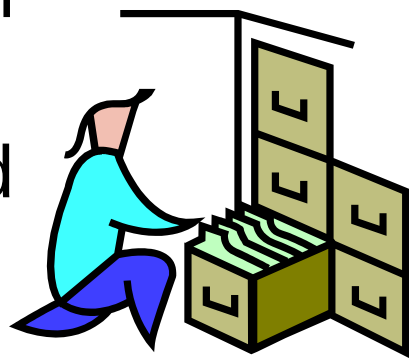
…Monitoring of Clinical Trials

- Sponsor must have written monitoring procedures (SOPs) to assure the quality of the study and ensure that each person involved carries out their duties
- SOPs should include:
  - How often will visits occur
  - Who will attend
  - What will be reviewed
  - How will problems be resolved
  - Communication flow

Record Retention Requirements

(21 CFR 312.57 and 21 CFR 312.62)

- Applies to investigational drug records, investigator financial interest records, and patient case histories (medical record and case report forms)
- Retain records and reports for 2 years after a marketing application is approved for the drug
- If NDA application is not approved, retain records and reports until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified



Disposition of Unused Drug

- Sponsor must ensure the return or destruction of all unused supplies of drug from each investigator

FDA Review of NDA or BLA

- FDA's approval is based on pre-clinical, manufacturing & clinical data in the NDA or BLA
  - Good Laboratory Practice (GLP)
  - Good Manufacturing Practice (GMP)
  - Good Clinical Practice (GCP)

Resources

- Code of Federal Regulations, Title 45 Part 46: Protection of Human Subjects
- Food and Drugs: Title 21
  - 21 CFR 312: IND Application
  - 21 CFR 314: NDA application
- Guidelines for Good Clinical Practice. International Conference on Harmonisation (ICH)

Evaluation

Please complete the evaluation form and fax to Elizabeth Ness at 301-496-9020.

For questions, please contact Elizabeth Ness
301-451-2179
nesse@mail.nih.gov